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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/072,767	02/07/2002	Brian Lee Batley	A0000403-01-JP	2919
28880	7590	11/04/2003	EXAMINER	
WARNER-LAMBERT COMPANY 2800 PLYMOUTH RD ANN ARBOR, MI 48105				SULLIVAN, DANIEL M
ART UNIT		PAPER NUMBER		
		1636		

DATE MAILED: 11/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
10/072,767	BATLEY ET AL.
Examiner	Art Unit
Daniel M Sullivan	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 18 August 2003.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-6,8-12,14-25 and 50 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-6,8-12,14-20,22-24 and 50 is/are rejected.

7) Claim(s) 21 and 25 is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ .
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .	6) <input type="checkbox"/> Other: _____ .

DETAILED ACTION

This Office Action is a reply to the "Amendment" filed 18 August 2003 (hereinafter, 18 August Paper) filed in response to the Non-Final Office Action mailed 24 February 2003 (hereinafter, 24 February Office Action). Claims 1-12, 14-25, 29-40 and 42-50 were considered in the 24 February Office Action. Claims 7, 29-40 and 42-49 were canceled and claim 1 was amended in the 18 August Paper. Claims 1-6, 8-12, 14-25 and 50 are pending and under consideration.

Response to Amendment

Rejection of claims 7, 29-40 and 42-49 is rendered moot by cancellation of the claims.

Claim Rejections - 35 USC § 103

Claims 1-6, 8-12, 14-20, 24 and 50 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Ullrich *et al.* in view of Hexdall *et al.* and in further view of Shibuya *et al.* and Murata *et al.* for reasons of record in Paper No. 2 and herein below in the response to arguments.

Claims 22 and 23 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Ullrich *et al.* in view of Hexdall *et al.* and further in view of Wcn *et al.* for reasons of record in Paper No. 2 and herein below in the response to arguments.

Claim Rejections - 35 USC § 112

Rejection of claims 1-6, 8-12, 14-25 and 50 under 35 U.S.C. 112, first paragraph, as lacking adequate written description is withdrawn in view of the amendment of the claims such that they are limited to comprising a gene encoding a phosphorylatable protein that can be phosphorylated by MAPK. Such proteins are conventional in the art and the skilled artisan would know which proteins would, more likely than not, be useful in the claimed method.

Response to Arguments

Claim Rejections - 35 USC § 103

In response to rejection of claims 1-6, 8-12, 14-20, 24 and 50 under 35 U.S.C. § 103(a) as unpatentable over Ullrich *et al.* in view of Hexdall *et al.* and in further view of Shibuya *et al.* and Murata *et al.*, Applicant first asserts that the teachings of Ullrich *et al.* fail to teach or suggest determining the amount of VEGF activity in a sample and provides no motivation to combine the disclosure of Ullrich *et al.* with Hexdall *et al.* (the 18 August Paper, page 6, third paragraph). These arguments have been fully considered but are not found persuasive. The instant claims are directed to "a method for determining vascular endothelial growth factor (VEGF) activity in a sample", which is precisely what the method of Ullrich *et al.* is designed to accomplish. Furthermore, the assertion that Ullrich *et al.* does not suggest determining the amount of VEGF activity in a sample appears to be at odds with other statements made in the same paragraph of Applicant's response. Specifically, Applicant states, "Ullrich is focused on using Flk-1 to identify compounds that are VEGF agonists or antagonists". Clearly, a method that is capable of identifying VEGF agonists or antagonists comprising assaying for activation of Flk-1 is also

capable of determining the amount of VEGF activity in a sample. Applicant's assertion that Ullrich *et al.* does not provide motivation to combine the teachings is not persuasive because, as pointed out in previous Office Actions (e.g., the Office Action mailed 5 June 2002, paragraph bridging pages 11-12) Ullrich *et al.* teaches engineering various cell lines to be used for screening VEGF agonists and antagonists, and then using those cell lines to assay for VEGF activity in a sample. Given this teaching, the skilled artisan would be motivated to do just that. Furthermore, the skilled artisan would be motivated to engineer the cell line disclosed by Hexdall *et al.* according to the teachings of Ullrich *et al.* because the reporter system of Hexdall *et al.* offers improved performance for adaptation to high-throughput applications (Hexdall *et al.*, page 2, second full paragraph). Therefore, the art, viewed as a whole, clearly provides motivation to combine the teachings disclosed therein according to the instant claimed invention.

Next, Applicant argues that Hexdall *et al.* does not suggest VEGF related assays, and does not teach or suggest that an assay to quantify bioactive VEGF could be obtained or be desirable. Applicant argues that Hexdall *et al.* provides no suggestion to transfect the cells described therein with a VEGF receptor, much less that such cells would have the beneficial properties taught in applicants' specification. This argument is not found persuasive because teachings specifically directed to VEGF are clearly set forth in Ullrich *et al.* One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Furthermore, the test for obviousness does not require that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would

have suggested the claimed invention to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Next, Applicant again argues that, even if one had the motivation to combine the teachings of Ullrich *et al.* and Hexdall *et al.*, one of ordinary skill in the art would not have a reasonable expectation that the combination of a VEGF receptor expression vector, a chimeric transactivation vector and a reporter vector as described in the claimed invention would be useful in determination of VEGF activity in a sample. To support this position, Applicant cites teachings from Shibuya *et al.* and Murata *et al.*, which were cited in the First Office Action on the Merits as teaching coupling of Flk-1 to the MAP kinase and ELK-1. Specifically, Applicant cites teachings from Shibuya *et al.* indicating that activation of the MAP kinase pathway is more efficient in endothelial cells than in NIH 3T3 cells. While Applicant's point is taken to the extent that stimulation was found to peak more rapidly in endothelial cells than in NIH 3T3 cells, the teaching does not suggest in any way that the cell line of Hexdall *et al.*, which is demonstrated to comprise a MAPK signaling pathway capable of activating ELK-1 and providing reporter gene expression upon activation of ELK-1 (see the 24 February Office Action, page 5), would not respond to VEGF simulation when engineered to express a VEGF receptor. In contrast, the teaching of Shibuya *et al.* demonstrates activation of the MAP kinase pathway in two cell types having dramatically different phenotypic characteristics. Thus, if anything, the teaching cited by Applicant suggests that VEGF coupling to the MAP kinase signaling pathway can be achieved in a wide variety of cell types. With regard to the Murata *et al.*, Applicant urges that the skilled artisan would not expect that the claimed invention would be suitable for determination of VEGF activity in a sample in view of teachings from Murata that indicate complexity of VEGF

signaling. This argument is not found persuasive because the teachings of Murata *et al.* and Shibuya *et al.* clearly demonstrate coupling of VEGF to activation of Elk-1. Given these teachings, and the teachings from Hexdall *et al.* demonstrating that activation of Elk-1 can be readily detected using the Elk-1 reporter cell line disclosed therein, one of ordinary skill in the art could reasonably expect that expression of a VEGF receptor in the Elk-1 reporter cell line would provide a cell capable of detecting VEGF activity in a sample, and thus useful in a method for determining VEGF activity in a sample. It is further noted that in the response to the rejection under 35 U.S.C. §112, first paragraph, Applicant argues, “use of other chimeric transactivators would not be expected to result in loss of the benefits of the invention, i.e., substitution of another appropriate chimeric transactivator would not be expected to disrupt the signaling chain” (page 8). This statement would seem at odds with the assertion that the complexity of VEGF signaling precludes a reasonable expectation of success in successfully coupling VEGF to a signaling system (i.e., ELK-1) in HeLa cells. It would seem that if the art is sufficiently predictable that one or ordinary skill in the art would have a reasonable expectation of success in practicing the claimed invention with a chimeric transactivator comprising any gene encoding a protein that can be phosphorylated by MAP kinase, one would also have a reasonable expectation of success in practicing the claimed invention with a transactivator comprising FLK-1 in HeLa cells.

Applicant’s arguments have been fully considered but are not found persuasive either individually or as a whole. Therefore, the claims stand rejected under 35 U.S.C. §103 as obvious over the art.

In response to rejection of claims 22 and 23 under 35 U.S.C. § 103(a) as unpatentable over Ullrich *et al.* in view of Hexdall *et al.* and further in view of Wen *et al.* Applicant argues that claim 22 is patentable over the references cited for reasons set forth regarding claim 1, from which it depends. This argument is not found persuasive for the reasons set forth herein above.

With regard to claim 23, Applicant further argues that while Wen *et al.* teaches activation of VEGF receptor within the claimed range of VEGF concentrations, it does not teach that such activation is sufficient in HeLa cells transformed with a VEGF receptor and the other recited elements. Applicant asserts that mere activation of Elk-1 would not have necessarily resulted in the efficient generation of signal required for a particularly useful assay. This argument is not found persuasive because it asserts that the skilled artisan would not have a reasonable expectation that activation of Elk-1 and expression of the reporter gene in the HeLa cells of Hexdall *et al.* would correlate with activation of the VEGF receptor. There is nothing on the record that would suggest that the cell line of Hexdall *et al.* would be any less sensitive to activation of the VEGF than the HUVEC cells of Wen. Thus, the skilled artisan would have a reasonable expectation of success of practicing the method wherein the VEGF activity is detectable at a VEGF concentration range between approximately 1 ng/mL to approximately 200 ng/mL. Therefore, the subject matter of claim 23 would be obvious to one of ordinary skill in the art at the time the invention was made and the claim stands rejected under 35 U.S.C. §103 as obvious over the art of record.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DMS


Daniel M. Sullivan
PRIMARY EXAMINER